Importance of Antimicrobial Stewardship in Solid Organ Transplant Recipients – an ESCMID Perspective

Running head: Antimicrobial stewardship in SOT

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/tid.13852.

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Abstract word count: 248

Text word count: 2177

Number of figures: 0

Number of tables: 0

Number of references: 51

Author contribution statement: PI, SK and DPK wrote the original draft and JS, TK, EC, VVP critically reviewed the manuscript.

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Proposed tweet: Application of known antimicrobial stewardship principles, biomarkers and new molecular rapid diagnostic tests can help rationalize antimicrobial prescribing in solid organ transplant recipients.

Abstract

Background: In the last decades, solid organ transplantation (SOT) has emerged as an important method in the management of chronic kidney, liver, heart and lung failure. Antimicrobial use has led to a significant reduction of morbidity and mortality due to infectious complications among patients with SOT, however, it can lead to adverse events and drive the development of antimicrobial resistance, thus, antimicrobial stewardship is of extreme importance. Even though there are ongoing efforts of transplant societies to implement principles of antimicrobial stewardship in everyday practice in SOT, there is still a lack of guidelines in this patient population. Aim: The aim of this study was to review the status of antimicrobial stewardship in patients with SOT, highlight its importance from the perspective of an ongoing vivid dialogue among ESCMID experts in the field of antimicrobial stewardship, and depict opportunities for future study in the field. Review: Antimicrobial stewardship programs are important in order to allow appropriate initiation and termination of antimicrobials in SOT recipients, and also aid in the most appropriate dosing and choosing of the route of administration of antimicrobials. Application of already known antimicrobial stewardship principles and application of currently used biomarkers and newly developed molecular rapid diagnostic testing tools can aid to the rationalization of antimicrobial prescribing and to a more targeted treatment of infections. Finally, physicians caring for SOT recipients should be actively involved in antimicrobial stewardship in order to assure optimization of antimicrobial prescribing and become familiar with the principles of antimicrobial stewardship.

Keywords: antimicrobial stewardship; transplantation; antimicrobial resistance; antibiotics

Introduction

In the last decades, solid organ transplantation (SOT) has emerged as an important method in the management of chronic kidney, liver, heart and lung failure. This has been supported by the improvement of surgical technique and post-operative pharmacological care that have led to a significant improvement of quality of life and prolongation of survival for these patients with immunosuppression being the most important factor for graft survival.[1–3] However, infections have ever since evolved as an important cause of morbidity and mortality in these patients.[4–9] Thus, antimicrobial use has changed the natural course of the post-transplantation period of patients receiving SOT. The risk of infection depends on the type and timing of transplantation including also donor-derived infections. However, due to the adverse events associated with inappropriate antimicrobial use including gastrointestinal dysbiosis, *Clostridioides difficile* infection (CDI), haematological complications, and other end-organ toxicities, along with the increasing antimicrobial resistance noted worldwide, antimicrobial stewardship programs (ASPs) have been established in several countries and are also required in some countries by regulatory authorities.

The aim of antimicrobial stewardship is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, selection of pathogenic organisms (such as *Clostridium difficile*), and emergence of resistance as well as reduce health care costs without adversely impacting quality of care.[10]

However, immunocompromised hosts are usually colonised and infected by multidrug-resistant organisms (MDROs) with limited treatment options, making the implementation of ASPs

challenging. This is also due to the complexity of these patients, the difficulty in establishing timely diagnosis of infectious complications, as well as the high mortality rate of these infections.[11,12]

There is evidence suggesting that antimicrobial stewardship practices can be implemented in patients with cancer and there is sparse similar evidence in patients with hematopoietic stem cell transplantation (HSCT). However, there is no clear such evidence in patients with SOT, even though due to the increased use of broad spectrum antimicrobials in this patient population there are multiple opportunities for collaboration with oncologists and transplant teams in order to improve selection, dosing and duration of antimicrobial agents..[13–15]

The aim of this study was to review the status of antimicrobial stewardship in patients with SOT, highlight its importance from the perspective of an ongoing vivid dialogue among ESCMID experts in the field of antimicrobial stewardship, and depict opportunities for future study in the field.

The need for reasonable use of antimicrobials

Patients with SOT are frequently receiving antimicrobials due to their complicated medical and surgical histories and they need immunosuppression in order to avoid transplant rejection. SOT recipients are at increased risk of MDR pathogen infections due to host-, donor-related factors, type and timing of transplantation. Antimicrobial use is often needed, however, in some instances, their use involves broader spectrum and longer duration than necessary. Inadequate medical prophylaxis in terms of indication, dose and duration, as well as infection by multidrug-resistant (MDR) bacteria, viral and fungal pathogens commonly affect patients with SOT and are associated with a very high mortality after transplantation.[16–19] Increased duration of antimicrobial use may promote antibacterial resistance even for a small duration of the administration of the antimicrobial.[20] On the

other hand, antimicrobial use is directly associated with development of CDI which can be associated with development of failure of the transplant and may also increase the likelihood of mortality.[20,21]

Current condition in antimicrobial stewardship in SOT

Even though there are ongoing efforts of transplant societies to implement principles of antimicrobial stewardship in everyday practice in SOT, there is still a lack of guidelines in this patient population.[22,23] On the other hand, perceptions of physicians involved in the care of patients with immunosuppression regarding infection severity and appropriateness may influence their attitude on the value of antimicrobial stewardship.[23] Involvement of infectious diseases specialists in the management of patients with SOT is associated with better implementation of antimicrobial stewardship practices and has led to improved patient outcomes.[24,25] Ideally, infectious diseases specialists should be collaborating with infectious diseases pharmacists with experience in SOT recipients, oncologists and transplant teams in order to optimize the efforts of antimicrobial stewardship. A relatively recent study that involved audits on all antimicrobial therapy in patients with transplantation assessed each antimicrobial regimen against stewardship principles that were established by the Centers for Disease Prevention and Control supplemented by transplant-specific infection guidelines. This study identified opportunities for antimicrobial stewardship in transplant recipients, and more specifically, among those patients that did not require a consultation by infectious diseases.[25] In another study performed in the USA, a voluntary survey was performed in order to gauge current antimicrobial stewardship practices in patients with transplantation, evaluate the availability and usefulness of novel diagnostics and identify challenges for implementation of antimicrobial stewardship practices. This study revealed that these practices were already performed in many adult and pediatric transplant centers in the USA, even though diagnostic and therapeutic uncertainty remained challenging for antimicrobial stewardship practices.[26]

Furthermore, optimization of antifungal drug prescribing by prescribing the antifungal according to the prevailing indication, diagnostic testing and therapeutic drug monitoring has shown to be successful and is endorsed by national guidelines for immunosuppressed patients.[22] Regarding cytomegalovirus (CMV), improvement of route, timing and dosing of specific antiviral agents has been associated with better outcomes regarding CMV infection.[27]

Potential objectives in SOT recipients

Appropriate agent selection is of utmost importance, given the increased mortality that is associated with delays in appropriate therapy in SOT recipients with infection.[28] Multidrug resistance rates in patients with SOT are higher than in other patients.[29] Thus, it is important to be aware of the possibility of increased antimicrobial resistance in this patient population and, if possible, the local microbiology and the patterns of antimicrobial resistance in order to make appropriate choices of antimicrobial agents. Thus, empirical therapy should be based on guidelines and antimicrobial resistance patterns, and this could aid towards to reduction of inappropriate antimicrobial use, while, de-escalation should be performed based on the culture results whenever possible. Furthermore, timely discontinuation of antimicrobial treatment in patients empirically treated for infection when no evidence of infection arises could also aid towards to reduction of unnecessary antimicrobial consumption. Another important issue regarding antimicrobial use is the identification of the correct dose of antimicrobials for each patient, depending on the renal function, as, under-dosing of antimicrobials could be associated with therapeutic failure, while, on the other hand, over-dosing could be associated with unnecessary antimicrobial use with associated toxicity.[30–32]

Preauthorization of restricted antimicrobials as well as prospective audit and feedback are recommended as basic intervention policies regarding antimicrobial stewardship by national guidelines and they have shown remarkable efficacy.[22] There are no adequate high quality published

reports evaluating the effect of the abovementioned interventions in SOT recipients, however, they are among the most common practices in transplant centers.[26] For example, in a Canadian transplant center, prospective audit and feedback in SOT recipients had as a result the improvement of antimicrobial prescribing.[25] Even though there are no studies in patients with SOT recipients, there is evidence suggesting that using a list of restricted antimicrobials could be associated with a reduction in nosocomial infection rates, length of stay, and costs and possibly also with a reduction in mortality, even though, this remains to be examined in this specific patient population.[30]

Intravenous-to-oral switch should be performed whenever possible, also in SOT recipients. Even though this may be recommended in transplant centers, real life transition rates are largely unknown.[22,26] Beyond antibacterial agents, intravenous to oral transition could also be applied to other agents, such as antivirals and antifungals, such as in the case of ganciclovir to valganciclovir in non-severe CMV infection.[33,34]

The role of pharmacokinetics and pharmacodynamics in dosing optimization is established in specific antibacterials and antifungals in SOT recipients and the same principles in antiviral agents are currently further explored.[22,35]

Therapeutic drug monitoring of antimicrobial agents is very important in SOT recipients and target levels of antiviral agents for CMV prophylaxis are increasingly recognized and have been recently studied in kidney transplant recipients.[36] Furthermore, interventions from pharmacists, such as clinical guidance on dose optimization have been associated with earlier therapy, less frequent CMV infections and lower resistance to gancoclovir.[37,38]

Guidelines for specific infections

Use of guidelines is commonly applied in transplant centers and they can prove to be potent tools in implementing an antimicrobial stewardship program.[26] Guidelines should lead to reduction of

inappropriate prescribing by including updated evidence-based recommendations. They should specify the appropriate route of administration of antimicrobial as well as the duration of treatment.[39] For example, similar outcomes were noted in a mixed population that included SOT patients when shorter courses of antimicrobials were administered for uncomplicated bacteremia by Gram-negative microorganisms, including *P. aeruginosa*.[40,41] Another example has to do with recent guidelines regarding enterococcal infections in SOT recipients, where suggestions now favor stopping antimicrobial therapy in non-endocarditis cases where blood cultures are negative, source control has been achieved and patients are clinically stable.[16]

Antimicrobial prophylaxis

Unnecessary antimicrobial use could be avoided to some extent in the peri- and post-transplantation period, as in the case of antimicrobial prophylaxis. For example, there are differences between different transplant centers in the post-transplantation prophylaxis, as well as in regards to the transplanted organ. Auditing adherence to the recommended antimicrobial scheme as well as the duration of its use in perioperative antimicrobial prophylaxis could be implemented in order to reduce unnecessary antimicrobial use. Furthermore, the universal use of antifungal prophylaxis is being or has been debated recently. For example, in a Canadian study, performing bronchoalveolar lavage (BAL) and linking this to a pre-emptive strategy based on galactomannan is used to prevent invasive aspergillosis in patients with lung transplantation has led to a 50% decrease of exposure to antimicrobials.[42] Thus, there are opportunities for reduction of antimicrobial use in the post-transplantation period through personalized treatment.

Diagnostic tools and antimicrobial stewardship

In order to timely and accurately diagnose infectious complications in patients with SOT, rapid diagnostics are routinely used. Their use can lead to reduction of inappropriate overuse, misuse or underuse of antimicrobials.[22] Among these tools, the use of galactomannan in serum and BAL and respiratory viral panels are the most widespread and useful.[26]

Biomarkers have long been used in SOT recipients; however, their role remains unclear. For example, even though procalcitonin is been commonly used in guiding antimicrobial use discontinuation in patients with respiratory tract infections, in SOT recipients, immunosuppression may alter the results of this biomarker, thus, limiting its reliability.[43] Furthermore, serum galactomannan and β-D-glucan can be used as biomarkers in the diagnosis and the pre-emptive therapy of invasive aspergillosis, however, their value in SOT recipients may be limited, even though, galactomannan in BAL is considered of higher value.[25,44] These biomarkers could be used in an individualized way so to implement antimicrobial stewardship practices by achieving appropriate discontinuation of treatment in SOT recipients.

On the other hand, rapid diagnostic testing that includes matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry as well as peptide nucleic acid fluorescent in-situ hybridization (PNA-FISH) are commonly used in transplant centers, as they have been found to perform well in SOT recipients.[26,45] Furthermore, use of multiplex PCR panels can help in the identification of specific microorganisms and even aid in the knowledge of antimicrobial susceptibility through genetically identifying specific patterns of resistance. This can aid in antimicrobial stewardship, as it can rapidly provide information regarding choosing appropriate antimicrobial therapy.[26] T2Biosystems' T2Candida and T2Bacteria are molecular rapid diagnostic testing tools that can detect *Candida* and bacteria from whole blood by combining PCR and nuclear magnetic resonance spectroscopy, thus, providing high sensitivity in clinical studies.[46] Combination of the available utilities of molecular rapid diagnostic testing with standard antimicrobial

stewardship practices can lead to adequate rationalization of the use of antimicrobials; however, these utilities are copious and are not universally available.[47]

Knowledge of antimicrobial prescribing practices

It is of utmost importance to understand the knowledge, perceptions and practices of antimicrobial prescribing if an antimicrobial stewardship program is to be implemented.[48–50] This also applies in the case of SOT recipients.[23,39] It is not uncommon for practicing physicians caring for SOT recipients to overuse antimicrobials in this patient population since overestimation of benefits and underestimation of possible risks of antimicrobial treatment may be common.[51] Thus, understanding the local antimicrobial prescription practices and the knowledge and perceptions of physicians caring for SOT recipients may be a very helpful tool to identify potential targets for antimicrobial stewardship.

Conclusions

Antimicrobial stewardship programs are of extreme importance in order to allow appropriate initiation and termination of antimicrobials in SOT recipients, and also aid in the most appropriate dosing and choosing of the route of administration of antimicrobials. Application of already known antimicrobial stewardship principles and application of currently used biomarkers and newly developed molecular rapid diagnostic testing tools can aid to the rationalization of antimicrobial prescribing and to a more targeted treatment of infections. Finally, physicians caring for SOT recipients, should be actively involved in antimicrobial stewardship in order to assure optimization of antimicrobial prescribing and become familiar with the principles of antimicrobial stewardship.

Funding: This research has not received funding from any source.

Conflict of Interest: The authors declare no conflict of interest.

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